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Published in:
Head and Neck: Journal of the Sciences and Specialties of the Head and Neck

DOI:
10.1002/hed.21642

Publication date:
2011

ORAL SQUAMOUS CELL CARCINOMA AND A CLINICALLY NEGATIVE NECK: THE VALUE OF FOLLOW-UP

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Accepted 6 September 2010
Published online 29 November 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21642

Abstract: *Background.* In squamous cell carcinoma of the oral cavity (SCCOC), regular follow-up comprises 5 years of prescheduled visits, irrespective of tumor stage/classification and/or treatment. We analyzed our standard treatment and follow-up protocol in patients with a preoperative clinically negative neck (cN0) in SCCOC.

Methods. This is a retrospective chart analysis. Inventarization of treatment, occult metastatic spread, and follow-up were performed.

Results. In all, 197 patients were included. The occult metastatic rate was 24%. Eighty-three percent of recurrent disease presented within 2 years. Fifty-three percent of the patients with recurrent disease visited their physician outside prescheduled control visits.

Conclusions. Ultrasound-guided fine-needle aspiration cytology currently is 1 of the most reliable staging techniques in cN0 SCCOC. Regular follow-up could perhaps be limited from 5 to 2 years of prescheduled follow-up visits. © 2010 Wiley Periodicals, Inc. *Head Neck* **33:** 1400–1405, 2011

Keywords: neck dissection; follow-up; clinically negative neck; squamous cell carcinoma; oral cavity

One of the most controversial items in head and neck remains the treatment of the clinically negative neck (cN0) in squamous cell carcinoma of the oral cavity (SCCOC) attributed to the presence of occult metastases. Control of the primary tumor can usually be achieved by surgery and, in some cases, by radiotherapy. Tumor treatment failure is often attributed to metastatic spread to cervical lymph nodes, reducing survival by approximately 50%.[1–3] Management of the cN0 neck is therefore considered crucial. Three options are available: elective neck dissection, primary radiotherapeutic treatment, or a "wait-and-see" policy. The rationale behind the latter is that 60% to 80% of patients who undergo elective neck dissection are in fact being overtreated, leading to increased morbidity. A wait-and-see policy requires careful monitoring of the neck over time, in combination with ultrasound and/or ultrasound-guided fine-needle aspiration cytology (FNAC). Should a positive lymph node be detected during follow-up, different types of salvage neck dissection can be performed. With this strategy, some studies have found recurrence rates comparable to those for elective treatment of the neck.[4,5]

However, other studies (which did not include ultrasound-guided FNAC during follow-up for the neck) reported lower survival rates in patients following a wait-and-see policy,[6,7] compared with patients treated by elective neck dissection.

Given these considerations, we have first evaluated the results of our standard surgical treatment with elective neck dissection for patients suffering from SCCOC. Furthermore, we especially focused on the recurrence rate of regional disease following elective neck dissection, with special emphasis on the follow-up schedule that is advocated in the national guideline for oral carcinoma issued by the Dutch Cancer Society.

MATERIALS AND METHODS

In this retrospective study, the medical records of all consecutive patients with histologically proven SCCOC, who presented at the Radboud University Nijmegen Medical Center between January 1, 1992, and December 1, 2004, were reviewed. Patients with a cN0 neck staged through palpation and ultrasound who underwent selective neck dissection of levels I–III (supraomohyoidal neck dissection [SOHND]), as described by Medina et al,[8] as a staging procedure and as part of their treatment, were included. In all cases, a preoperative ultrasound examination of the

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neck was performed. If a suspicious lymph node (or nodes) with a minimum diameter >5 mm was found by ultrasound, fine-needle aspiration cytology was performed. A conventional chest x-ray was performed in every patient. CT and/or MRI scanning were performed only in case of doubts concerning primary tumor extension (eg, bone involvement). Patients who had had head and neck squamous cell carcinoma (HNSCC) 5 years prior to their current treatment or who had received radiotherapeutic or chemotherapeutic treatment for any kind of disease during this period were excluded.

Surgery was performed by 5 experienced head and neck surgeons. In the majority of cases, a frozen stage section of the neck specimen was performed during the operation: suspicious nodes and/or the largest jugulodigastric and most distal jugulo-omohyoid node were sampled. If frozen stage section during the operation revealed metastatic disease, selective neck dissection of levels I–III was routinely extended to a modified radical neck dissection (MRND), encompassing levels I–V. After the resection specimen had undergone standardized marking, it was sent to the department of pathology where it was examined using standardized sectioning and hematoxylin and eosin staining.

The detection of $\geq$2 histopathologically confirmed metastatic lymph nodes and/or the presence of extracapsular spread (ECS) were absolute indications for postoperative radiotherapeutic treatment. Tumor-positive resection margins were an indication for radiotherapeutic treatment of the primary site. Relative indications for postoperative radiotherapeutic treatment were: tumor invasion of the mandible, 1 metastatic lymph node, close resection margins (<5 mm), angiolymphatic invasion, perineural invasion, and a diffuse pattern of tumor growth. Local recurrence is defined as a recurrence at the original site within 5 years following therapeutic excision. After this time, local tumor growth is considered to be a secondary primary tumor. Regional recurrence is defined as metastatic neck disease that does not affect structures of the oral cavity. Distant metastasis is defined as tumor spread from the primary tumor to distant organs or distant lymph nodes (eg, not the neck).

The recommended follow-up comprises 5 years of regular prescheduled visits.[9] The minimum follow-up period in this study was 5 years. Our standard follow-up schedule consisted of visits every 2 months during the first year after surgical treatment, every 3 months during the second year, every 4 months during the third year, and every 6 months during the fourth and fifth years. Hereafter, in the absence of any signs of recurrence or metastatic spread, patients were discharged.

Survival curves were estimated with the Kaplan–Meier approach based on overall survival (OS) and disease-free survival (DFS). OS was calculated from the date that patients were surgically treated, whereas DFS was calculated using the date of detection of recurrent disease. Log-rank tests were used to compare the study groups.

RESULTS

In all, 197 patients were included: 125 men (63%) and 72 women (37%). Their age ranged from 27 to 90 years at the time of their operation (mean age, 62 years). Distributions of T and N classifications and tumor locations are shown in Table 1.

All patients were preoperatively staged cN0 through palpation and ultrasound. In 50 of 197 cases (25%; 220 necks) ultrasound-guided FNAC was performed. A total of 48 neck specimens (24% of patients) showed regional metastatic spread during postoperative histopathologic examination; 1 specimen was bilaterally positive (49 pN+ necks).

In a total of 30 T3 and T4 tumors, 5 times a Thiersch graft was used to close the site of the excised primary tumor. In 16 cases, extensive reconstructive surgery of the primary site was performed: 10 free-flap soft tissue transfers were performed, as were 6 bone reconstructions, combined with soft tissue reconstructions. In 9 of these 30 cases, the wound could be closed primarily.

In total, 76 metastases were found in 48 patients. No metastatic nodes were found in additionally resected neck levels (levels IV and V), performed after positive frozen stage section. Histopathologic staging of the neck yielded the following findings: 149 pN0, 33 pN1, 14 pN2b, and 1 pN2c (68 stage I, 63 stage II, 36 stage III, and 30 stage IVA tumors).

Twenty-two patients had absolute indications for postoperative radiotherapeutic treatment based on their neck staging (7 patients had 1 metastasis with ECS, 4 patients had $\geq$2 metastatic lymph nodes with

Table 1. Preoperative clinical TNM classification and location of 197 primary tumors.

Clinical TNM classification	No. of tumors by tumor site					
	Retromolar trigone	Floor of the mouth	Lateral tongue	Alveolar process	Buccal mucosa	Total
TxN0M0	0	1	1	0	0	2
T1N0M0	8	18	33	2	1	62
T2N0M0	7	47	41	4	4	103
T3N0M0	0	6	10	1	0	17
T4N0M0	5	4	0	4	0	13
Total	20	76	85	11	5	197

Table 2. Distribution of clinical and pathological TNM stages in 40 patients with recurrent disease.

	No. of tumors										
cTNM	pT1N0	pT2N0	pT3N0	pT4N0	pT1N1	pT2N1	pT4N1	pT2N2b	pT3N2b	pT4N2b	Total
TxN0M0	0	0	0	1	0	0	0	0	0	0	
T1N0M0	4	3	0	1	2	0	0	0	0	0	
T2N0M0	2	10	0	0	1	4	0	5	0	0	
T3N0M0	0	1	1	0	0	0	0	0	1	0	
T4N0M0	0	1	0	1	0	0	1	0	0	1	
Total	6	15	1	3	3	4	1	5	1	1	40

ECS, and 11 patients had >2 tumor-positive nodes). Fifteen of these 22 patients actually received postoperative radiotherapeutic treatment (1 of the remaining 7 patients died shortly after surgery as a result of massive aspiration, and the condition of the other 6 patients was too poor to administer adequate treatment). Sixty-two patients received radiotherapeutic treatment based on primary tumor characteristics.

Forty patients (20%) suffered from local, regional, or distant recurrence. For an overview of their respective cT and pTN stages/classifications, see Table 2. Fourteen of these patients initially presented with regional recurrence (7% of 197 patients). Of 149 pN0 necks, 9 patients (6%) developed initial regional recurrent disease, whereas 3 of the 48 patients with pN+ necks (6%) initially presented with regional recurrence. In 1 of these 12 patients, level IV (combined with level III) showed metastatic disease. Two more patients presented with regional recurrent disease, but also had a secondary primary tumor and the origin of regional disease was unclear. Six of 30 patients who had undergone extensive reconstructive surgery had recurrence: 3 local recurrences and 3 regional recurrences.

Twenty-four patients initially presented with a local recurrence (12% of 197 patients), whereas the remaining 2 patients had distant metastatic disease, only without locoregional residual disease.

Fourteen of the 40 patients with recurrent disease were palliatively treated (35%). Nineteen patients with recurrent disease underwent salvage surgery, and 9 of these patients also received radiotherapeutic treatment. Six patients received curative radiotherapeutic treatment. One patient was treated in a different hospital for recurrent disease and was lost to follow-up.

Of the 19 patients treated by salvage surgery, with or without additional radiotherapeutic treatment, 11 died of recurrent disease (58%), a further 2 died of a second primary tumor, and 1 died of an unrelated disease. Five of these 19 patients were disease-free at the end of follow-up. All 6 patients treated with curative intent by radiotherapy died of recurrent disease. In total, 17 of 25 curatively treated patients (68%) died because of recurrent disease, 5 were alive and free of disease at the end of follow-up, 2 died from second primary tumors, and 1 patient died as a result of cardiovascular disease. This means that 20 of 25 patients (80%) were dead within 5 years of treatment for recurrent disease; in other words, 78% of patients presenting with recurrent disease died a tumor-related death.

The mean follow-up duration was 46 months (3.8 years; median, 60 months; minimum, 0 months; maximum, 60 months). The mean time between primary curative surgery and appearance of recurrent disease was 15 months (1.25 years; median, 10 months; minimum, 2 months; maximum, 58 months). Eighty percent of recurrences appeared within 20 months after primary curative surgery, 83% within 2 years from treatment, and 90% within 3 years from treatment.

In terms of presentation of recurrent disease, 16 patients (40%) presented with signs of recurrent disease during prescheduled routine visits. Twenty-one patients (53%) visited their oncologist at their own request with symptoms related to their recurrent disease, and for 3 patients (7%) it was not possible to ascertain when the recurrent disease was detected in these patients.

Finally, Figures 1 and 2 show the overall survival and disease-free survival, respectively, in cN0 SCC of the oral cavity. Five-year overall survival was 67% (Figure 1). Five-year disease-free survival was 93, 80, 85, and 63% in stages I–IVA, respectively (Figure 2).

DISCUSSION

Our results confirm that, to date, selective neck dissection of levels I–III (formerly SOHND) remains the most important diagnostic tool in clinically N0 squamous cell carcinoma of the oral cavity. In a widely accepted proposed treatment strategy, Weiss et al[10] estimate that if there is a >20% probability of finding occult metastatic spread during histopathologic examination of cN0 necks in SCC of the oral cavity, elective treatment of the neck should be performed. The preoperative use of ultrasound-guided FNAC combined with standard histopathologic examination of the dissection specimen revealed a comparable percentage of occult metastases, compared with preoperative staging by CT, MRI, or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG–PET) followed by histopathologic staging,[4,5,11–15] although its use is still not widely accepted. This finding has been previously

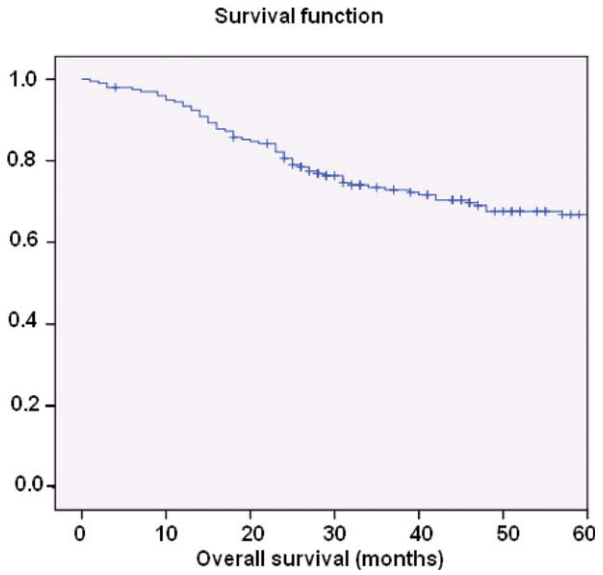

FIGURE 1. Cumulative overall survival (months). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

mentioned by authors, such as van den Brekel et al[4,5] and Nieuwenhuis et al,[16] who even propose a wait-and-see policy for a cN0 neck in certain cases of head and neck SCC.

In the current study, the percentage of occult metastatic spread and recurrent disease is comparable to previously published data.[12,14,17]

Six percent of patients with a pN0 neck as well as 6% of patients with a pN+ neck developed an initial regional recurrence. If more sensitive histopathologic techniques would have been used (for instance, the use of immunohistochemistry and improved serial sectioning), perhaps more pN+ necks would have been identified. Selective neck dissection would then have been even more therapeutic than we think since those necks, scored pN0, do not show more recurrent disease than pN+ necks, of which most are additionally treated.

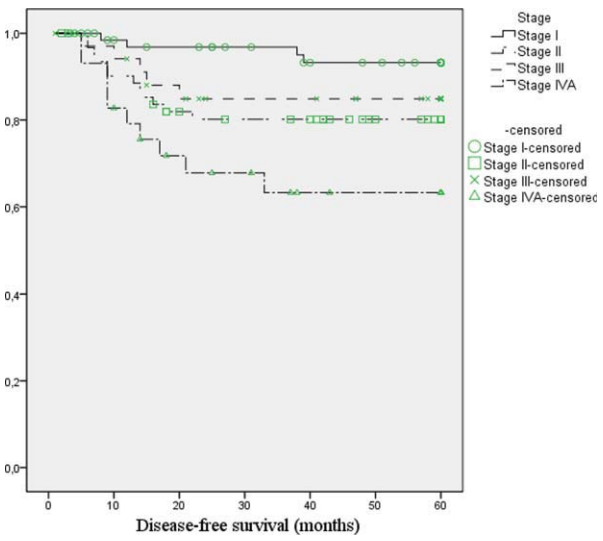

FIGURE 2. Cumulative disease-free survival (months) related to postoperative tumor stage. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

We found no so-called skip metastases in our neck dissection specimens: of course, aforementioned limitations of standard histopathologic workup could also influence these numbers. Furthermore, only 1 initial regional recurrence involved level IV and, thus, in this group of patients, addition of level IV to standard treatment of the neck (as proposed by a number of authors[21,22]) does not seem justified. With postoperative radiotherapeutic treatment on indication, this group with cN0 SCCOC has a 5-year DFS of 83%.

The main goal of strict follow-up schedules would be to signal recurrent disease at an early stage, preferably leading to more successful salvage treatment. More than half of the patients who had recurrent disease made an extra appointment that led to the detection. Despite salvage treatment, however, survival rates decline dramatically with recurrent disease. This leads to questions regarding the follow-up schedule proposed in the Dutch national guideline for oral cavity carcinoma issued by the Dutch Cancer Society. For example, could prescheduled visits be limited? Could patients be better informed about the signs of possible recurrent disease and could regular visits even be abandoned?

In terms of costs, 76% of patients in this study with cN0 oral cavity carcinoma underwent elective treatment of the neck without any signs of postoperative metastatic spread. In all, 124 of 197 patients (63%) remained disease-free postoperatively during follow-up. In other words, 63% of patients were intensively followed during the course of 5 years, involving high costs. Van den Brekel et al[5] showed that in a group of mainly T1 and T2 oral tumors strict follow-up of the neck using ultrasound-guided FNAC every 2 to 5 visits (prescheduled visits every 4–8 weeks during the first year) could possibly replace elective neck dissection. In terms of our cohort, this would imply a total of 992 visits (8 visits per year on average), 310 ultrasounds (2.5 per year on average), and at least as many FNA biopsies in 124 disease-free patients during the first year of follow-up alone. Of course, in the case of more advanced c- and pTN classifications/stages, especially after extensive reconstructive surgery, we would prefer to see the patient on a frequent basis because of a higher chance at postoperative complications, a more prolonged recovery time, and probably a higher need of psychosocial assistance.

The use and duration of follow-up has been questioned over the past few decades.[23–27] Not only in SCCOC, but also in other fields of medicine, has it been shown that prescheduled follow-up visits probably do not improve chances at more early detection

of recurrent disease. For instance, Ritoe et al[27] showed that for laryngeal cancer treated primarily by radiotherapy, only 2% of the total number of routine visits revealed subclinical recurrent disease.

Follow-up after curative treatment of oral carcinoma has a number of goals: early identification of recurrent disease or second primary tumors and early curative treatment if possible, psychosocial help, registration of late complications following therapy, and evaluation of treatment. The value of follow-up depends largely on certain parameters such as whether a feasible treatment for recurrent disease is available, whether early detection improves patient survival, and whether there is a proper diagnostic test (eg, good sensitivity/specificity) to rule out recurrent disease.

If we consider these parameters in the context of our study, we have shown that our treatment for recurrent disease saves only 22% of patients with recurrent disease. Our study shows that over half of patients with recurrent disease visit their treating surgeon outside the prescheduled visits. Finally, the diagnostic tests are the same as those used during preoperative staging (inspection, palpation, and ultrasound-guided FNAC) and have the same limitations. Five of 197 patients benefited from the detection of their recurrent disease as they survived after salvage treatment. Three of these 5 recurrences were detected at prescheduled follow-up visits, and 2 were detected at extra visits at the patients' own request. The necessity and cost-effectiveness of a routine follow-up schedule can thus be questioned, given that there is a very limited effect on survival. However, from a psychosocial perspective (for instance, rehabilitation after extensive surgery), routine follow-up is, of course, valuable, as well as in the evaluation of complications and treatment, especially in patients who underwent extensive reconstructive surgery. Merkx et al[9] have already called for a reduction in the number of years of follow-up from 10 to 5 years. We would suggest that in curatively treated oral carcinoma, especially in low-stage tumors, the number of years of routine follow-up could perhaps be reduced from 5 to 2 years as a next step in limiting prescheduled doctor visits.

CONCLUSIONS

Selective neck dissection of level I–III remains a reliable staging procedure in cN0 SCCOC and appears to have therapeutic value as well. There is no indication for a level IV dissection. In case of recurrent disease, survival rates drop dramatically despite treatment. Long-term routine follow-up in case of cN0 oral SCC is of very limited benefit in terms of patient survival and could perhaps be limited to 2 years, leading to more cost-effective postoperative treatment.

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